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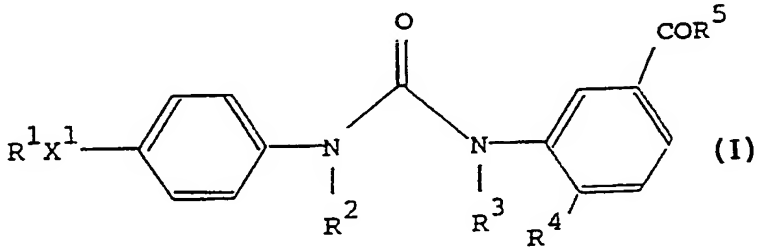

(I)

(57) Abstract

Diphenylurea derivatives of formula (I), wherein R^1 represents alkyl, X^1 represents oxygen, $-OCH_2-$ or $-S(O)_n-$, wherein n is zero, 1 or 2, R^2 and R^3 each represents hydrogen, methyl or ethyl, R^4 represents alkyl, dimethylamino, $-OR^6$ or $-S(O)_mR^6$, wherein m is zero, 1 or 2 and R^6 represents alkyl optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, and R^5 represents $-NR^7R^8$ or $-OR^9$, wherein R^7 and R^8 each represents hydrogen or alkyl optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, and R^9 represents alkyl optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms possess useful pharmacological properties.

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"DIPHENYLUREA DERIVATIVES"

This invention relates to new, therapeutically useful diphenylurea derivatives, to a process for their production and to pharmaceutical compositions containing them, and methods for their use.

The new diphenylurea derivatives of the present invention are the compounds of formula I, hereinafter depicted, wherein R^1 represents a straight- or branched-chain alkyl group containing from about 4 to about 18 carbon atoms, X^1 represents an oxygen atom, or a group of the formula $-OCH_2-$ or $-S(O)_n-$, wherein n represents zero, 1 or 2, R^2 and R^3 may be the same or different and each represents a hydrogen atom or a methyl or ethyl group, R^4 represents a straight- or branched-chain alkyl group containing up to about 6 carbon atoms, a dimethylamino group or a group of the formula $-OR^6$ or $-S(O)_mR^6$, wherein m represents zero, 1 or 2 and R^6 represents a straight- or branched-chain alkyl group containing up to about 6 carbon atoms, optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, preferably an alkyl, alkenyl, alkoxyalkyl, alkylthioalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing up to about 6 carbon atoms, and R^5 represents a group of the formula $-NR^7R^8$ or $-OR^9$,

wherein R^7 and R^8 may be the same or different and each represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to about 6 carbon atoms, optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, preferably an alkyl, alkenyl, alkoxyalkyl, alkylthioalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing up to about 6 carbon atoms, and R^9 represents a straight- or branched-chain alkyl group containing up to about 6 carbon atoms, optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, preferably an alkyl, alkenyl, alkoxyalkyl, alkylthioalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing up to about 6 carbon atoms.

As will be apparent to those skilled in the art, some of the compounds of formula I exhibit optical isomerism. All such forms, and their mixtures, are embraced by the invention.

Especially important compounds of the present invention include those wherein at least one of the symbols has a value selected from the following:-

(i) R^1 represents an alkyl group containing

from 8 to 12, e.g. 9, 10 or 11, carbon atoms;

((i) X^1 represents an oxygen atom;

(iii) R^2 and R^3 each represents a hydrogen atom;

(iv) R^4 represents an alkyl, alkoxy or alkylthio group containing 1 or 2, preferably 1, carbon atoms;

(v) R^7 represents a hydrogen atom;

(vi) R^8 represents a straight- or branched-chain alkyl group containing up to 5, preferably 3 or 4 carbon atoms, optionally interrupted by an oxygen or sulphur atom, preferably an alkyl, alkoxyalkyl or alkylthioalkyl group containing up to 5, preferably 3 or 4 carbon atoms; and/or

(vii) R^9 represents an alkyl group containing up to 3 carbon atoms, e.g. a methyl group;

the other symbols being as hereinbefore defined.

Important compounds according to the invention include:-

A N-(4-decyloxyphenyl)-N'-[2-methylthio-5-(2-methylthioethylcarbamoyl)phenyl]urea;

B N-(4-decyloxyphenyl)-N'-(2-methoxy-5-methoxy-carbonylphenyl)urea;

C N-(4-decyloxyphenyl)-N'-[2-methoxy-5-(2-methoxy-ethylcarbamoyl)phenyl]urea;

D N-(4-decyloxyphenyl)-N'-[2-methoxy-5-(2-methylthioethylcarbamoyl)phenyl]urea;

E N-(5-N-butylcarbamoyl-2-methoxyphenyl)-N'-(4-decyloxyphenyl)urea;

F N-(5-N-butylcarbamoyl-2-methylthiophenyl)-N'-(4-decyloxyphenyl)urea;

G N-(5-N-butylcarbamoyl-2-methoxyphenyl)-N'-(4-undecyloxyphenyl)urea;

H N-(5-N-butylcarbamoyl-2-methylphenyl)-N'-(4-nonyloxyphenyl)urea;

I N-(5-methoxycarbonyl-2-methylthiophenyl)-N'-(4-nonyloxyphenyl)urea;

J N-[2-methylthio-5-(2-methylthioethylcarbamoyl)-phenyl]-N'-(4-nonyloxyphenyl)urea;

K N-[2-methylthio-5-(2-methylthioethylcarbamoyl)-phenyl]-N'-(4-undecyloxyphenyl)urea; and

L N-(5-N-butylcarbamoyl-2-methylphenyl)-N'-(4-undecyloxyphenyl)urea.

The letters A to L are allocated to compounds for easy reference later in this specification.

The compounds according to the invention are inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT;EC 2.3.1.26). They are therefore of value as anti-atherosclerotic agents and have utility in the treatment of atherosclerosis, hyperlipidaemia,

depicted, wherein R^1 and X^1 are as hereinbefore defined, optionally prepared in situ, by the application or adaptation of known methods.

The reaction between the compound of formula II and the compound of formula III preferably takes place in a suitable solvent, for example dichloromethane, toluene, or a mixture thereof. The reaction preferably takes place at an elevated temperature, for example at or near 100°C.

Preparation of the intermediate of formula III in situ can be carried out by the reaction of a compound such as bis(trichloromethyl) carbonate with a compound of the general formula IV, hereinafter depicted, wherein R^1 and X^1 are as hereinbefore defined. The reaction is preferably carried out in a solvent such as toluene, in the presence of a tertiary amine, e.g. triethylamine, preferably at an elevated temperature.

According to a further feature of the invention, compounds of formula I are prepared by reacting a compound of general formula:

$$R^9OH \qquad (V)$$

wherein R^9 is as hereinbefore defined, or a compound of general formula:

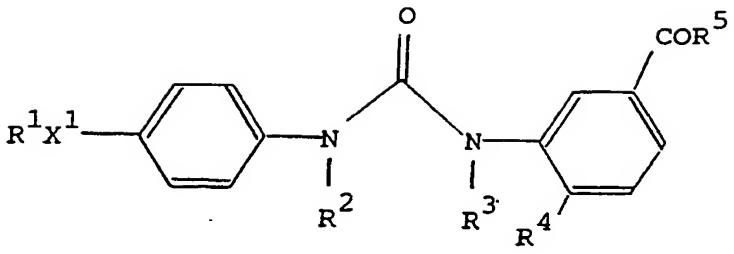
$$HNR^7R^8 \qquad (VI)$$

wherein R^7 and R^8 are as hereinbefore defined, with a compound of formula VII, hereinafter depicted, wherein R^1, R^2, R^3, R^4 and X^1 are as hereinbefore defined and Z^1 represents a halogen, e.g. chlorine, atom, preferably in the presence of a base, such as a tertiary amine and optionally in a solvent, e.g. toluene, optionally with heating.

According to a further feature of the invention, compounds of formula I wherein at least one of m and n is zero may be converted into a compound of formula I wherein m and/or n is greater than in the starting material, the other symbols being as hereinbefore defined, by oxidation using a conventional oxidant, such as a percarboxylic acid (e.g. m-chloroperbenzoic acid), in an inert solvent, such as dichloromethane, at or below room temperature.

According to a further feature of the invention, compounds of general formula I are prepared by the interconversion of other compounds of formula I. For example, compounds of formula I wherein R^2 and/or R^3 and/or R^7 and/or R^8 is other than a hydrogen atom may be prepared from compounds of formula I wherein R^2 and/or R^3 and/or R^7 and/or R^8 represents a hydrogen atom by the application or adaptation of known methods of alkylation.

Compounds of formulae II, III, IV, V, VI and VII may be prepared by the application or adaptation of known methods.



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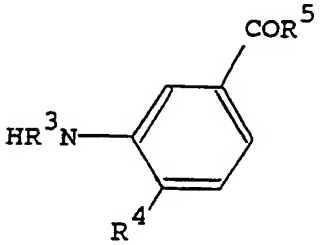

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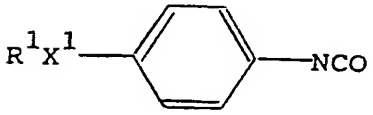

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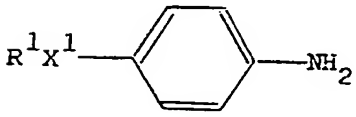

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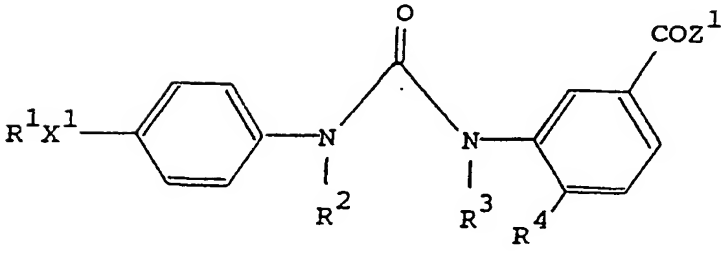


VII

The following Examples illustrate the preparation of the compounds according to the invention and the Reference Example illustrates the preparation of the intermediates.

EXAMPLE 1

Compounds A and B

A stirred solution of bis(trichloromethyl) carbonate (0.49g) in toluene (100ml) was treated with a suspension of 4-decyloxyaniline (1.24g) and triethylamine (0.7ml) in toluene (150ml) at the ambient temperature under an inert atmosphere. The mixture was stirred for 30 minutes and then was heated at 100°C for 2 hours. The mixture was then cooled and evaporated, and the resulting residue was dissolved in dichloromethane (200ml). This solution was treated with 3-amino-4-methylthio-N-(2-methylthioethyl)-benzamide (1.1g) and the mixture was heated at reflux for 1 hour. The mixture was then allowed to stand at the ambient temperature for 18 hours, and then it was washed with water (100ml), dried over magnesium sulphate, and concentrated under reduced pressure to a volume of about 50ml when a solid separated. This solid was filtered off and recrystallised from ethanol, to give N-(4-decyloxyphenyl)-N'-[2-methylthio-5-(2-methylthioethylcarbamoyl)phenyl]urea (1.3g) in the form of small colourless needles, m.p. 126-128°C.

Elemental analysis:- C,63.5;H,7.9;N,8.10;S,12.00%; calculated:- C,63.24;H,7.77;N,7.90;S,12.06%;].

By proceeding in a similar manner, but using methyl 3-amino-4-methoxybenzoate in place of the 3-amino-4-methylthio-N-(2-methylthioethyl)benzamide, there was prepared N-(4-decyloxyphenyl)-N'-(2-methoxy-5-methoxycarbonylphenyl)urea in the form of colourless crystals, m.p. 115-116°C. [Elemental analysis:- C,68.50;H,8.1;N,5.98%; calculated:- C,68.39;H,7.95; N,6.13%].

EXAMPLE 2

Compounds C, D and E

A mixture of N-(5-carboxy-2-methoxyphenyl)-N'-(4-decyloxyphenyl)urea (1.55g; prepared as described in Reference Example 1) and thionyl chloride (0.27ml) in toluene (60ml) was heated at reflux for 30 minutes. The mixture was then chilled and added dropwise, with cooling, to a stirred solution of 2-methoxyethylamine (0.8g) in toluene (20ml). The mixture was allowed to stand at the ambient temperature for 18 hours, and then it was evaporated and the resulting residue was extracted with hot dichloromethane (3x50ml). The extract was evaporated and the residue was recrystallised from acetone, to give N-(4-decyloxyphenyl)-N'-

[2-methoxy-5-(2-methoxyethylcarbamoyl)phenyl]urea (0.75g) in the form of a colourless powder, m.p. 126-128°C. [Elemental analysis:- C,67.70;H,8.4; N,8.50%; calculated:- C,67.31;H,8.27;N,8.41%].

By proceeding in a similar manner, but using the appropriate quantities of 2-methylthioethylamine and butylamine in place of the 2-methoxyethylamine, there were prepared:-

N-(4-decyloxyphenyl)-N'-[2-methoxy-5-(2-methylthioethylcarbamoyl)phenyl]urea in the form of colourless crystals, m.p. 105-107°C (from methanol) [Elemental analysis:- C,65.20;H,8.00;N,8.2;S,6.10%; calculated:- C,65.21;H,8.01;N,8.15;S,6.22%]; and

N-(5-N-butylcarbamoyl-2-methoxyphenyl)-N'-(4-decyloxyphenyl)urea, in the form of off-white crystals, m.p. 62-63°C [purification by mplc on silica gel, eluting with a mixture of diethyl ether and methanol (19:1v/v)] [Elemental analysis:- C,69.80;H,8.80;N,8.40%; calculated:- C,69.99;H,8.71;N,8.44%].

EXAMPLE 3

Compound F

A stirred solution of bis(trichloromethyl) carbonate (0.49g) in toluene (100ml) was treated with a suspension of 4-decyloxyaniline (1.24g) and triethylamine (0.7ml) in toluene (150ml) at the ambient temperature under an inert atmosphere and stirred for

30 minutes. The mixture was heated at 100°C for 5 hours. The mixture was treated with 3-amino-N-butyl-4-(methylthio)benzamide (1.19g) and stirring was continued at 100°C for a further period of 2 hours. The mixture was allowed to stand at the ambient temperature for 18 hours, and then it was diluted with dichloromethane (500ml), washed with hydrochloric acid (2x100ml;2N), dried over magnesium sulphate, and then evaporated. The resulting residue was dissolved in a hot mixture of ethyl acetate and ethanol (150ml;1:1v/v). Upon cooling, a solid separated out and was discarded. The remaining filtrate was concentrated under reduced pressure to a volume of about 50ml, when a second solid separated. This second solid was recrystallised from ethanol, to give N-(5-N-butylcarbamoyl-2-methylthio-phenyl)-N'-(4-decyloxyphenyl)urea (0.65g), in the form of a colourless solid, m.p. 110-112°C. [Elemental analysis:- C,67.60;H,8.5;N,7.90%; calculated:- C,67.80; H,8.44;N,8.18%].

EXAMPLE 4

Compounds G, H, I, J, K and L

A stirred solution of bis(trichloromethyl) carbonate (0.99g) in toluene (200ml) was treated with 4-undecyloxyaniline (2.63g) at the ambient temperature under an inert atmosphere. The suspension was then treated with triethylamine (2.79ml), resulting in a

N-(5-methoxycarbonyl-2-methylthiophenyl)-N'-(4-nonyloxyphenyl)urea in the form of tiny colourless needles, m.p. 155-157°C (from ethanol) [Elemental analysis:- C,65.10;H,7.50;N,5.80%; calculated:- C,65.47;H,7.47; N,6.11%];

N-[2-methylthio-5-(2-methylthioethylcarbamoyl)phenyl]-N'-(4-nonyloxyphenyl)urea in the form of a colourless solid, m.p. 120-123°C (from ethyl acetate) [Elemental analysis:- C,62.40;H,7.80;N,7.70%; calculated:- C,62.63;H,7.59;N,8.12%];

N-[2-methylthio-5-(2-methylthioethylcarbamoyl)phenyl]-N'-(4-undecyloxyphenyl)urea in the form of a colourless solid, m.p. 130-131°C (from ethanol) [Elemental analysis:- C,64.1;H,8.2;N,7.4%; calculated:- C,63.82; H,7.94;N,7.70%]; and

N-(5-N-butylcarbamoyl-2-methylphenyl)-N'-(4-undecyloxyphenyl)urea in the form of a colourless solid, m.p. 159-164°C (from ethyl acetate) [Elemental analysis:- C,72.25;H,9.2;N,8.3%; calculated:- C,72.69;H,9.15; N,8.48%].

REFERENCE EXAMPLE 1

A suspension of N-(4-decyloxyphenyl)-N'-(2-methoxy-5-methoxycarbonylphenyl)urea (10.67g) and sodium hydroxide (1.02g) in a mixture of ethanol (250ml) and water (25ml) was heated at reflux for 90 minutes. The mixture was then cooled, acidified by

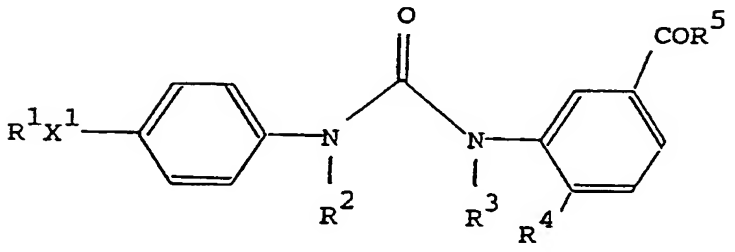
The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, rectally or orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also include capsules of absorbable material such as

CLAIMS

1. A diphenylurea derivative of the formula:



I

wherein R^1 represents a straight- or branched-chain alkyl group containing from 4 to 18 carbon atoms, X^1 represents an oxygen atom, or a group of the formula $-OCH_2-$ or $-S(O)_n-$, wherein n represents zero, 1 or 2, R^2 and R^3 may be the same or different and each represents a hydrogen atom or a methyl or ethyl group, R^4 represents a straight- or branched-chain alkyl group containing up to 6 carbon atoms, a dimethylamino group or a group of the formula $-OR^6$ or $-S(O)_mR^6$, wherein m represents zero, 1 or 2 and R^6 represents a straight- or branched-chain alkyl group containing up to 6 carbon atoms, optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, and R^5 represents a group of the formula $-NR^7R^8$ or $-OR^9$, wherein R^7 and R^8 may be the same or different and each represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 6 carbon atoms, optionally containing one

or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms, and R^9 represents a straight- or branched-chain alkyl group containing up to 6 carbon atoms, optionally containing one or more carbon-carbon double bonds, and optionally interrupted by one or more hetero atoms.

2. A compound according to claim 1 wherein R^6 and R^9 each independently represents an alkyl, alkenyl, alkoxyalkyl, alkylthioalkyl, alkylaminoalkyl, or dialkylaminoalkyl group containing up to 6 carbon atoms and R^7 and R^8 each independently represents a hydrogen atom or an alkyl, alkenyl, alkoxyalkyl, alkylthioalkyl, alkylaminoalkyl, or dialkylaminoalkyl group containing up to 6 carbon atoms.

3. A compound according to claim 1 or 2 wherein at least one of the symbols has a value selected from the following:-

(i) R^1 represents an alkyl group containing from 8 to 12 carbon atoms;

(ii) X^1 represents an oxygen atom;

(iii) R^2 and R^3 each represents a hydrogen atom;

(iv) R^4 represents an alkyl, alkoxy or alkylthio group containing 1 or 2 carbon atoms;

(v) R^7 represents a hydrogen atom;

(vi) R^8 represents a straight- or branched-chain alkyl group containing up to 5 carbon atoms, optionally

interrupted by an oxygen or sulphur atom; and/or

(vii) R^9 represents an alkyl group containing up to 3 carbon atoms;

the other symbols being as hereinbefore defined.

4. A compound according to claim 3 wherein R^1 represents an alkyl group containing 9, 10 or 11 carbon atoms; R^4 represents an alkyl, alkoxy or alkylthio group containing 1 carbon atom and R^8 represents a straight- or branched-chain alkyl group containing up to 5 carbon atoms optionally interrupted by an oxygen or sulphur atom; and R^9 represents methyl.

5. A compound according to any one of the preceding claims wherein R^8 represents an alkyl, alkoxyalkyl or alkylthioalkyl group containing 3 or 4 carbon atoms.

6. A compound according to claim 1 which is

N-(4-decyloxyphenyl)-N'-[2-methylthio-5-(2-methylthioethylcarbamoyl)phenyl]urea;

N-(4-decyloxyphenyl)-N'-(2-methoxy-5-methoxycarbonylphenyl)urea;

N-(4-decyloxyphenyl)-N'-[2-methoxy-5-(2-methoxyethylcarbamoyl)phenyl]urea;

N-(4-decyloxyphenyl)-N'- [2-methoxy-5-(2-methylthioethylcarbamoyl)phenyl]urea;

N-(5-N-butylcarbamoyl-2-methoxyphenyl)-N'-(4-decyloxyphenyl)urea;

N-(5-N-butylcarbamoyl-2-methylthiophenyl)-N'-(4-decyloxyphenyl)urea;

N-(5-N-butylcarbamoyl-2-methoxyphenyl)-N'-(4-undecyloxyphenyl)urea;

N-(5-N-butylcarbamoyl-2-methylphenyl)-N'-(4-nonyloxyphenyl)urea;

N-(5-methoxycarbonyl-2-methylthiophenyl)-N'-(4-nonyloxyphenyl)urea;

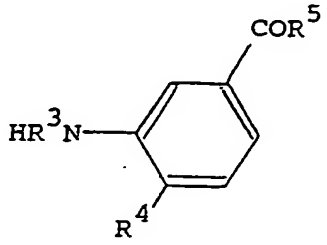
N-[2-methylthio-5-(2-methylthioethylcarbamoyl)-phenyl]-N'-(4-nonyloxyphenyl)urea;

N-[2-methylthio-5-(2-methylthioethylcarbamoyl)-phenyl]-N'-(4-undecyloxyphenyl)urea; or

N-(5-N-butylcarbamoyl-2-methylphenyl)-N'-(4-undecyloxyphenyl)urea.

7. A process for the preparation of a diphenylurea derivative according to claim 1 which comprises:

(A) when R^2 represents a hydrogen atom and the other symbols are as defined in claim 1, the reaction of a compound of the general formula:



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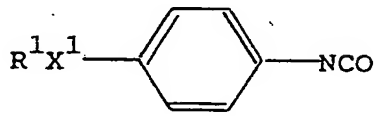
wherein R^3, R^4 and R^5 are as defined in claim 1 with a compound of the general formula :



III

wherein R^1 and X^1 are as defined in claim 1, which compound is optionally prepared in situ;

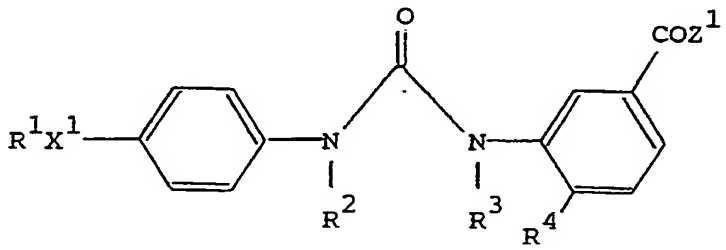
(B) the reaction of a compound of the general formula:

$$R^9OH \qquad V$$

wherein R^9 is as defined in claim 1, or a compound of the general formula :

$$HNR^7R^8 \qquad VI$$

wherein R^7 and R^8 are as defined in claim 1, with a compound of the general formula :



VII

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01383

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 C 323/63 C 07 C 323/42 A 61 K 31/24
C 07 C 275/42 A 61 K 31/17 C 07 C 273/18

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
	No relevant documents have been disclosed.	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06-11-1991	23. 12. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

REMARK: Although claim 10 is directed to a method of treatment of the human/ animal body the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.